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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/260,037	03/02/1999	ORON YACOBY-ZEEVI	00/20442	6023

7590 03/28/2006

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/260,037	YACOBY-ZEEVI, ORON	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of claim 73 and the addition of new claims 75-80 in the paper of 12/12/2005, is acknowledged. Applicants' arguments filed on 12/12/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Claims 71-80 are still at issue and are present for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of claims 71 and 72 for containing new matter was made in the previous office action and is repeated below for applicants convenience.

Applicants previous amendment of claim 71 (claim 72 dependent from) which recites "...none of said somatic mammalian cells in said preparation is genetically

modified to express heparanase" is not supported by the specification at the time of filing and thus considered new matter.

Applicants continue to argue this rejection on the basis that the subject application necessarily shows that exemplified cells are not genetically modified to express heparanase and the examiner has not met the burden of explaining why this disclosure is not adequate. Applicants further argue that to satisfy the written description requirement, disclosure can be implicit or inherent.

As previously stated, while it is appreciated that applicants do describe species and examples of encompassed biological preparations that are not necessarily genetically modified cells, applicants do not have support for the **negative limitation** that none of said cells is genetically modified .

Using applicants logic, applicants could attempt to describe any of a number of limitations that were inherent to the disclosed examples, to carve out a claimed subgenus of biological preparations. The 112 first paragraph requirement for written description does not allow such. Applicants disclosure must support the newly claimed subgenus, which while applicants do disclose examples which fall within this subgenus, as well as an infinite number of additional subgenuses, applicants do not adequately describe the subgenus of those biological preparations in which "none of said cells is genetically modified to express heparanase."

The mere inherency or implicitness of a limitation is not necessarily adequately described without some showing that applicants were in possession of this newly claimed subgenus.

Applicants further argue that in the previous analysis of applicants possession, the examiner has missed the point, and that the point is not that the particular species and examples of cells described (which may or may not be genetically modified) but rather, the point is that the disclosure in the subject application is that heparanase is being added to the cell preparations and that this would necessarily mean that the cells are not genetically modified to over-express heparanase, for if they were so modified, why would heparanase be added.

Applicants further argue that applicants argument is not based on the inherent nature of the exemplified cells, but rather the context of applicants disclosure of adding heparanase, which necessarily implies that the exemplified cells are not genetically modified to express heparanase.

Applicants finally submit that there is no logical reason to genetically engineer cells to over-express heparanase when heparanase is already added to this preparation of cells and thus this is an absolute clear example of implied or inherent disclosure and therefore meets the requirement of written description.

Applicants complete argument is acknowledged and has been carefully considered, however, continues to be found nonpersuasive on the following basis. Applicants submission that the context of applicants disclosure of adding heparanase, necessarily implies that the exemplified cells are not genetically modified to express heparanase and that there is no logical reason to genetically engineer cells to over express heparanase when heparanase is already being added to this preparation of cells is unclear and not found persuasive.

Applicants argument is not persuasive on the basis that the mere expression of heparanase does not necessarily mean that the heparanase will be secreted so that it may then become externally adhered to the cells. Thus, under those situations in which the cells are genetically modified to express heparanase, but not so genetically modified to also secrete the expressed heparanase, it would make sense to externally add heparanase to such cells, given applicants logic. Thus applicants disclosure continues to not support that applicants were in possession of those cells in which none of said cells is genetically modified to express heparanase. Particularly in light of the claimed embodiments that include genetically modified cells, even those genetically modified to express heparanase.

Claims 71, 72, 75-78 are further rejected under this statue for containing new matter as the limitation of those biological preparations comprising "ex vivo somatic mammalian cells" are not supported by the specification at the time of filing and considered new matter. As discussed above for claims 71 and 72 applicants are requested to show support that applicants were in possession at the time of filing of those subgenuses of biological preparations drawn to cells which are "ex vivo", "somatic" and "mammalian".

This rejection was previously made to claims 71-74. In response to this rejection, applicants amended the claims and added new claims 75-80 and argue the rejection as it applies to the newly amended claims.

Applicants argue the rejection as it applies to the remaining claims. Applicants argue that new claim 75 is directed to ex vivo cells and support for such is found in the specification , for example at pages 38-54 and more particularly at page 48, lines 19-22. Applicants submit that this disclosure is implicit and that the skilled artisan would clearly understand that the exemplified cell preparations are *ex vivo*.

Applicants complete argument is acknowledged, however, not found persuasive on the basis that applicants mere disclosure of cultured bone marrow stromal cells (BMSC) does not support applicants limitation of "*ex vivo*".

Applicants argue that new claim 76 is directed to somatic cells and support for such is found in the specification , at page 35, lines 8, which uses the term "somatic" and makes clear that the claimed subject matter is somatic therapy.

Applicants complete argument is acknowledged, however, not found persuasive on the basis that applicants referred to passage is that of "a somatic gene therapy method of in vivo introduction of genetically modified cells..." This does not support applicants claim to "somatic cells".

Applicants argue that new claim 77 is directed to mammalian cells and support for such is found in the specification , for example at pages 16, lines 20, which uses the term "mammalian" as in "Mammalian embryo implantation". This does not make clear that the subject matter of the invention is mammalian tissue and cells.

Finally, based on the above, Claims 71, 72, 75-78 remain rejected under this statue for containing new matter as the limitation of those biological preparations comprising "exvivo", "somatic", "mammalian" and especially "ex vivo somatic

mammalian cells" are not supported by the specification at the time of filing and considered new matter. As discussed previously and above for claims 71 and 72 applicants are requested to show support that applicants were in possession at the time of filing of those subgenuses of biological preparations drawn to cells which are "ex vivo", "somatic" and "mammalian".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 73, 74, 76, 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Pecker et al. (U.S. Patent No. 5,968,822).

It is noted that this rejection was made previously, but withdrawn based upon applicants previous amendments. Applicants current amendments have necessitated the reapplication of this rejection.

Pecker et al. teach a polynucleotide encoding a human heparanase polypeptide. Pecker et al. further teach the infection of High Five or Sf21 cells with pFhpa virus and the expression of the encoded mammalian heparanase. Pecker et al. further teach that upon expression of the encoded mammalian heparanase, by the High Five or Sf21 cells

the heparanase is excreted into the medium, as demonstrated by the ability of the culture medium to produce low molecular weight HS degradation fragments upon incubation of the medium with sulfate-labeled ECM. Thus an inherent property of the insect cultures expressing the taught recombinant mammalian heparanase as taught by Pecker et al. is that the excreted heparanase would externally adhere to said cells, thereby increasing the natural amount of heparanase externally adhered to said cells, so as to enhance extravasation, implantation, transplantation, invasion and/or migration of said cells in vivo. Further these cells are genetically modified cells. Thus Pecker et al. anticipate claims 71 and 72.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 73, 74, 76, 77, 79, 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pecker et al. (U.S. Patent No. 5,968,822) and Weinshank et al. (U.S. Patent No. 5,360,735).

As discussed above, Pecker et al. teach a polynucleotide encoding a human heparanase polypeptide. Pecker et al. further teach the infection of High Five or Sf21 insect cells with pFhpa virus and the expression of the encoded mammalian heparanase. Pecker et al. further teach that upon expression of the encoded

mammalian heparanase, by the High Five or Sf21 cells the heparanase is excreted into the medium, as demonstrated by the ability of the culture medium to produce low molecular weight HS degradation fragments upon incubation of the medium with sulfate-labeled ECM. Thus an inherent property of the insect cultures expressing the taught recombinant mammalian heparanase as taught by Pecker et al. is that the excreted heparanase would externally adhere to said cells, thereby increasing the natural amount of heparanase externally adhered to said cells, so as to enhance extravasation, implantation, transplantation, invasion and/or migration of said cells in vivo. Further these cells are genetically modified cells. Pecker et al. further teach that the produced heparanase would be useful in various therapeutic applications and that host cell used to recombinant ly produce the mammalian heparanase can be of any type such as prokaryotic cell, eukaryotic cell, a cell line or a cell as a portion of a multicellular organism.

Weinshank et al. teach the cloning and expression of a human 5-HT_{1F} receptor nucleic acid into in a vector that comprises mammalian regulatory elements and the transfection of NIH-3T3 fibroblasts with said vector for the use of the produced 5-HT_{1F} receptor in various therapeutics.

One of skill in the art at the time of invention would have been motivated to express the mammalian heparanase cloned by Pecker et al. in a mammalian cell line so that the produced protein would be subjected to proper post-translational processing so that the protein produced recombinantly would be as close to that which naturally occurs as is possible. This motivation is especially high since Pecker et al. discusses

that ultimately the protein may be used for therapeutic applications. As discussed above, an inherent property of the cultures expressing the taught recombinant mammalian heparanase as taught by Pecker et al. is that the heparanase is excreted and would externally adhere to said cells, thereby increasing the natural amount of heparanase externally adhered to said cells, so as to enhance extravasation, implantation, transplantation, invasion and/or migration of said cells in vivo. One would have been so motivated to transfect the NIH 3T3 fibroblast cells, as used by Weinshank et al. with the mammalian heparanase cloned by Pecker et al. as a means of producing the mammalian heparanase in a mammalian cell line to ensure proper post-translational processing. The expectation of success was high as a result of the high level of knowledge in the art with respect to the cloning and expression of heterologous proteins in NIH 3T3 cells, as seen in the results of Weinshank et al. Thus claims 73-80 are made obvious over Pecker et al. and Weinshank et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1652

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3/1/2006